REMARKS

This responds to the Office Action dated January 28, 2010.

Claim 42 has been added. As a result, claims 2, 4, 8, 9, 10, 28, 29, 30, 31, 32, 37, 41 and 42 are now pending in this application.

Claim 41 has been amended by deleting reference to "proliferation" of cytotoxic T cells. Hence, claim 41 states that the antigenic peptide stimulates cytotoxic T cells. Support for stimulation of cytotoxic T cells by the antigenic peptide is present in the specification as filed, for example, at page 8, lines 14-22 and page 9, lines 15-20. Applicant submits that this amendment adds no new subject matter to the application.

Claim 42 has been added and recites that the method is carried out *in vitro*. Support for carrying the method out *in vitro* is present in the specification as filed, for example, in original claim 10 and at page 13, lines 6-9. Applicants submit that no new matter has been introduced into the application by new claim 42.

In addition, new claim 42 is novel and patentably distinct over WO 96/07432, for the same reasons as described below for claims 2, 4, 8-10, 28-32, 37 and 41. Claim 42 depends from and incorporates the subject matter of claim 2. Because WO 96/07432 fails to disclose key elements of claim 2 (and the other independent claims), WO 96/07432 fails to anticipate all of the pending claims, including claim 42. Moreover WO96/07432 fails to disclose that cytotoxic T cells should be added in any *in vitro* method.

Accordingly, claim 42 is novel and patentable in view of WO 96/07432, and Applicants respectfully request that the Examiner consider and allow the newly added claim 42.

The Rejection of Claims under § 112

Claim 41 has been rejected under 35 U.S.C. §112, first paragraph, as the specification allegedly does not contain a written description of the claimed invention. According to the Examiner, the specification at page 10 discloses proliferation of cytotoxic T cells only after stimulation with *foreign* antigens.

Applicants have deleted reference to "proliferation" of cytotoxic T cells from claim 41 solely to expedite the allowance of this application. Support for stimulation of cytotoxic T cells by the antigenic peptide is present in the specification as filed, for example, at page 8, lines 14-22 and

page 9, lines 15-20. Applicant submits that the specification clearly provides a written description of claim 41.

Withdrawal of this rejection of claim 41 under 35 U.S.C. § 112, first paragraph, is respectfully requested.

The Rejection of Claims under § 102

Claims 2, 4, 8-10, 28-32, 37 and 41 have been rejected under 35 U.S.C. 102(b) as allegedly anticipated by WO 96/07432. The Examiner alleges that WO 96/07432 discloses a method of expressing/presenting an antigenic molecule on the surface of a viable cancer cell and that the teachings of WO 96/07432 are not limited to the internalization of toxic molecules, nor to gene therapy nor to *in vitro* internalization.

Applicants submit that the Examiner is mixing passages from the WO 96/07432 inappropriately and that the scope of WO 96/07432 as it relates to treatment of cancer is different from the general disclosure of WO 96/07432 with respect to photochemical internalization. In essence, WO96/07432 provides a general disclosure on photochemical internalization and specific disclosure on treatment of cancer. However, the general disclosure on photochemical internalization fails to disclose key details of the elements of Applicants' claims while the specific disclosure on cancer treatment is limited to killing cancer cells by photochemical internalization of toxic molecules and/or DNA. Nowhere does WO96/07432 disclose anything, either generally or specifically, about using antigenic peptides in a photointernalization method to stimulate a cytotoxic T cell response. Nowhere does WO96/07432 disclose a method involving cancer cells that would inherently achieve cell surface expression or stimulation of a cytotoxic T cell response.

To serve as an anticipation when a reference is silent about the asserted inherent characteristic, the gap in the reference may be filled by recourse to extrinsic evidence. But, such evidence must make clear that "the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." *Continental Can Co. v. Monsanto Co.*, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991).

Here, the missing matter is not necessarily present in WO96/07432 and no one of skill in the art would recognize that WO96/07432 inherently discloses presentation of an antigenic

peptide on the surface of a viable cancer cell, which results in cytotoxic T cell mediated cell killing by a cytotoxic T cell specific for the antigenic peptide. The WO96/07432 disclosure on cancer treatment is very limited and fails to disclose anything whatsoever about presenting antigens on the surface of cells. Instead, WO96/07432 expressly teaches that the molecules are internalized within cells. By touting the benefits of the WO96/07432 photochemical internalization methods, the WO96/07432 teaches one of skill in the art that these methods result in *internalization* – not cell surface presentation of antigenic peptides.

Moreover, to solve the problems of treating cancer, the WO96/07432 disclosure only extends to internalizing toxic molecules and DNA. A teaching of killing cancer cells with a toxin is not a disclosure of Applicant's method of treating cancer. No presentation of an antigenic peptide on the surface of a viable cancer cell is possible under such circumstances. A brief generic disclosure of internalization of DNA is not a disclosure of a method of photochemically internalizing an antigenic peptide so that the peptide is presented on the cell surface resulting in cytotoxic T cell mediated killing of the cancer cell. Hence, WO96/07432 does not expressly or inherently disclose Applicants' claims because at least one element is missing from the WO96/07432 disclosure – presentation of an antigenic peptide on the surface of a viable cancer cell that results in cytotoxic T cell mediated cell killing of the cancer cell.

Applicant contends the Examiner's allegations are contrary to binding case precedent-- *In re Zurko* (258 F.3d 1379, 59 U.S.P.Q.2d 1693 (Fed. Cir. 2001)). In *Zurko*, the Patent and Trademark Office (PTO) rejected Zurko's claims where at least one of the claim limitations was not explicitly disclosed by the cited art; nevertheless, the PTO announced that such a limitation was inherent. See *id.* at 1695. In reversing the PTO, the Court held that the PTO cannot simply make such conclusions with respect to core factual findings in determining patentability. *Id.* at 1697. Instead, the Court required that the PTO 'point to some concrete evidence in the record' to support its findings concerning aspects of the relevant technology. *Id.*

The current facts are analogous. WO96/07432 is silent as to presentation of antigenic peptides on the cell surface of viable cancer cells and cytotoxic T cell mediated cell killing of the cancer cell. In fact the terms "antigen" and "T cell" cannot be found in the WO96/07432 disclosure. Thus, WO96/07432 fails to expressly disclose some of the limitations recited in claims 2, 4, 8-10, 28-32, 37 and 41. While the Examiner argues such limitations are inherent in

WO96/07432, such an allegation represents a core factual finding relevant to patentability of Applicants' claims. Applicant submits that the Examiner must 'point to some concrete evidence in the record' to support a finding of anticipation or this rejection must be withdrawn. Because WO96/07432 is silent with respect to antigen presentation after photochemical internalization and cytotoxic T cell mediated cell killing of the cancer cell, the Examiner has failed to establish anticipation.

These issues are discussed in more detail below.

WO96/07432 is concerned with an alternative to the known photodynamic therapy (PDT) method in which widespread cell death results from the generation of cytotoxic intermediates generated by light exposure (*see*, WO96/07432 page 1, line 15 to page 2, line 3). The language used in WO96/07432 shows that the majority of the cells are not killed by this photointernalization method (see page 1, first paragraph; page 2, lines 19-25; page 2, line 32 to page 3, line 8; page 6, lines 4-8). The percentage of cells that may be killed by this method is quantified in e.g. Example 1, which discloses 10-20% cell death by the photointernalization method alone. Thus, the WO96/07432 method allows molecules to be introduced into the cytosol of viable cells by photochemical internalization without significant cell death, and the photointernalization procedure does not destroy cells as does the PDT procedure.

The Examiner appears to rely on the more general disclosure of the specification to maintain the rejection, indicating that because the reference teaches the introduction of molecules into cells without killing them, and teaches the introduction of molecules into cancer cells that this is an anticipation of the present claims. However, a prior generic disclosure does not anticipate claims to a species because anticipation requires disclosure of each and every element of the claimed invention.[1] Applicants' claims are directed to a species of photointernalization procedures that were heretofore not contemplated by the prior art. No anticipation can be found because WO96/07432 fails to recite a method where an antigenic peptide is presented on the surface of a viable cancer cell, resulting in cytotoxic T cell mediated cell killing of the cancer cell.

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[1] *Bristol-Myers Squibb Company v. Ben Venue Laboratories Inc.*, 246 F3d 1368 (Fed. Cir. 2001) (vacating summary judgment of anticipation for method claims 6 and 9 because the prior art disclosed only the use of premedicants generally, not the specific classes of premedicants in those claims: steroids, antihistamines, and H2-receptor antagonists).

Moreover, according to WO96/07432, the photointernalization procedure alone fails to kill cells. Thus, when seeking to treat cancer, WO96/07432 teaches that more is needed than simply performing the photointernalization procedure. The WO96/07432 disclosure speaks directly to the issue as described below.

Disclosure by WO96/07432 of not killing cells merely concerns how photointernalization is conducted to avoid the generation of cytotoxic species resulting from photoactivation. WO96/07432 states in many places that the majority of the cells are not killed by the method (see page 1, first paragraph; page 2, lines 19-25; page 2, line 32 to page 3, line 8; page 6, lines 4-8). The percentage of cells which may be killed by this method are quantified, for example, in Example 1 which recites that 10-20% cell death occurs by the photointernalization aspect of the treatment alone. Thus WO96/07432 is concerned with an alternative to the known photodynamic therapy (PDT) method in which widespread cell death results from the generation of cytotoxic intermediates generated by light exposure (see, WO96/07432 page 1, line 15 to page 2, line 3). The WO96/07432 method therefore allows molecules to be introduced into the cytosol of viable cells by photochemical internalization rather than just destruction of those cells by PDT.

However, the limited cell death which occurs in the method described in WO96/07432 specifically relates to the death resulting from the cytotoxic species generated by the photochemical treatment. This is evident in several instances in the document. Page 1, line 3 refers to cell death resulting from "the photodynamic treatment." Example 1 shows that cell death is limited to 10-20% (and reduction in protein synthesis by 30-40%) when the photochemical internalization method alone is employed. Thus the specification and examples of WO96/07432 are clearly concerned with limiting the effects of the photochemical internalization method itself on cell functionality.

However, when describing treatment of cancer cells, where death of cancer cells is desired, WO96/07432 does not disclose use of the photochemical internalization method alone or use of any or all molecules in the photochemical internalization method. More significantly, WO96/07432 does not disclose an immunological solution to the problem of cancer treatment. WO96/07432 fails to disclose use of an antigenic peptide that is presented on the cell surface of a viable cancer cell following by cytotoxic T cell mediated cell killing. Instead, for treating

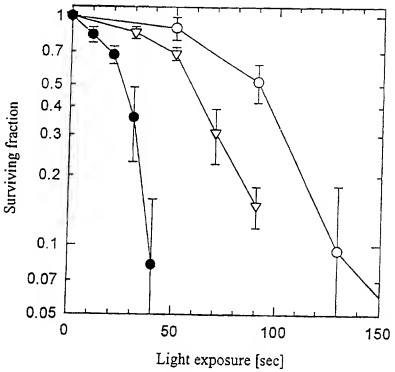
cancer, WO96/07432 is expressly limited to internalization of only a few types of molecules – none of which are peptide cancer antigens.

> 1) Cancer treatment.
> Several photosensitizers accumulate preferentially in neoplastic tissues, the selectivity for a tumor over the surrounding tissue being usually a factor of 2-3, but this factor may in some cases, such as for brain tissues, be higher, i.e. up to 30. Molecules which may be of clinical interest for treatment of cancer, but is restricted by a low or no uptake into the cytosol can be introduced into the cytosol by means of the present invention. Gelonin, as exemplified below, is an example of such a molecule. Several other molecules, either alone or linked to other molecules (e.g. antibodies, transferrin, photosensitizers, apoB on reconstituted LDL-particles) can be used. The advantage of such a combination treatment would be 1) enhanced cytotoxic effect in deeper layers of the tumor tissues since low and subtoxic doses of light are sufficient for disruption of lysosomes and endosomes; 2) enhanced specificity of the toxin since PDT is only given to the area of tumor localization. WO96/07432, page 7, lines 5-18.

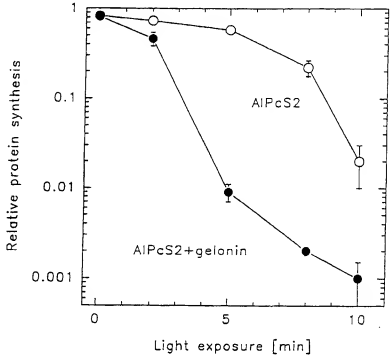
Thus, the disclosure of WO96/07432 with respect to cancer treatment is narrow, limited to molecules such as toxins, antibodies, transferrin, photosensitizers, and apoB on reconstituted LDL-particles.

The paragraph cited above is followed by a short disclosure relating to gene therapy. But such disclosure of DNA internalization does not anticipate Applicants' claims. Nowhere are antigenic cancer peptides mentioned or contemplated for cancer treatment by the WO96/07432 disclosure. Nor is there any mention of cell surface presentation of any antigenic peptide in the WO96/07432 disclosure. WO96/07432 fails to disclose methods that result in cytotoxic T cell killing of cancer cells.

Similarly, when illustrating use of the photointernalization procedure for cancer treatment in the Examples, WO96/07432 is specifically limited to internalization of toxic molecules. Thus, Example 1 of the WO96/07432 disclosure describes the amount of cancer cell death resulting from the action of the internalized plant toxin, as measured by inhibition of protein synthesis (see, page 8, lines 23-24 and Figure 2). Example 2 and Figure 3 (reproduced below) show the surviving fraction of cancer cells treated with gelonin as a function of light exposure (open circles = light only; open triangles and filled circles = different concentrations of gelonin).



Example 4 illustrates that transport of gelonin can be achieved without damaging the cells profoundly (page 10, lines 16-22), but it is clear from Figure 5 (reproduced below) that the use of gelonin (a cytotoxic peptide) profoundly affects the cell's viability (see also, line 19 on page 20).



Clearly, in methods in which cancer cells are treated, WO96/07432 is limited to use of toxins, and cell death occurs without presentation of an antigenic peptide on the surface of the cancer cells. The Examples show that that these methods achieve almost total cell death (see Figure 3, filled circles in which PCI+ gelonin is used). Dead cells cannot present peptides on their cell surface. The cells that are not dead remain viable only because the cytotoxic peptide has not been internalized and, hence, do not present antigen on the cell surface.

The teachings by WO96/07432 in relation to cancer are therefore limited and concern only methods in which cell death is the final result of the photointernalization method. As Applicants' claims relate to cancer cells, the only relevant disclosure by WO96/07432 is its teachings on cancer treatment. To suggest that the document teaches the use of other molecules for internalization into cancer cells goes beyond the disclosure of the document in relation to cancer. Furthermore, the cells disclosed by WO96/07432 are not in contact with cytotoxic T cells and thus the required feature of claim 2 cannot be achieved. Hence, Applicants submit that the teachings and examples provided in WO96/07432 fall outside the scope of Applicants' claims.

Nowhere does the specification disclose or suggest a method involving cancer cells in which the internalized molecules are antigenic peptides that are presented on the surface of cancer cells resulting in cytotoxic T cell mediated cell killing. Thus, WO 96/07432 fails to anticipate claims 2, 4, 8-10, 28-32, 37, 41 and 42 and the rejection under 35 U.S.C. 102(b) with respect to WO 96/07432 should be withdrawn.

CONCLUSION

Applicant respectfully submits that the claims are in condition for allowance, and notification to that effect is earnestly requested. The Examiner is invited to telephone the undersigned at (516) 795-6820 to facilitate prosecution of this application.

If necessary, please charge any additional fees or deficiencies, or credit any overpayments to Deposit Account No. 19-0743.

Respectfully submitted,

SCHWEGMAN, LUNDBERG & WOESSNER, P.A.
P.O. Box 2938
Minneapolis, MN 55402--0938
(516) 795-6820

Date May 28, 2010

By /Robin A. Chadwick/
Robin A. Chadwick
Reg. No. 36,477

CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being filed using the USPTO's electronic filing system EFS-Web, and is addressed to: Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on this 28th day of May, 2010.

PATRICIA A. HULTMAN
Name

Signature